-continued

<223> OTHER INFORMATION: Polypeptide sequence of anti-IL6R ICVD ID-54V

<400> SEQUENCE: 35

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Thr Arg Leu Thr Cys Lys Ala Ser Gly Ser Ile Phe Asn Ile Asn
            20                  25                  30

Ser Ile Asn Val Met Ala Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg
        35                  40                  45

Glu Leu Val Ala Ile Ile Gly Lys Gly Gly Gly Thr Asn Tyr Ala Asp
    50                  55                  60

Phe Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ala Ala Lys Asn Thr
65                  70                  75                  80

Val Asn Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Tyr Ala Asp Tyr Glu Asp His Asp Ser Pro Phe Asn Ala Ser
            100                 105                 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120
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1-63. (canceled)

64. A method of making a HIS-substituted immunoglobulin chain variable domain, wherein the method comprises:

(i) providing a progenitor immunoglobulin chain variable domain having an amino acid sequence comprising three complementarity determining regions (CDR1-CDR3) and four framework regions, wherein said progenitor immunoglobulin chain variable domain binds a target; and

(ii) substituting an arginine residue or a lysine residue with a histidine residue in one or more CDRs of said amino acid sequence to produce said HIS-substituted immunoglobulin chain variable domain comprising a HIS-substituted amino acid sequence, wherein said histidine residue is substituted for said arginine residue or said lysine residue in said one or more CDRs, wherein said HIS-substituted immunoglobulin chain variable domain has increased intestinal stability relative to said progenitor immunoglobulin chain variable domain.

65. The method of claim **64**, wherein step (ii) comprises substituting said arginine residue or said lysine residue with said histidine residue in two CDRs of said amino acid sequence.

66. The method of claim **64**, wherein step (ii) comprises substituting said arginine residue or said lysine residue with said histidine residue in only one CDR of said amino acid sequence.

67. The method of claim **64**, wherein step (ii) comprises substituting said arginine residue or said lysine residue with said histidine residue in CDR2 or CDR3.

68. The method of claim **67**, wherein step (ii) comprises substituting said arginine residue or said lysine residue with said histidine residue in only CDR2.

69. The method of claim **67**, wherein (ii) comprises substituting said arginine residue or said lysine residue with said histidine residue in only CDR3.

70. The method of claim **64**, wherein no more than one lysine or arginine residue is substituted.

71. The method of claim **64**, wherein the HIS-substituted immunoglobulin chain variable domain has increased intestinal stability in the duodenum, jejunum, ileum cecum, colon, rectum and/or anal canal, relative to the stability of said progenitor immunoglobulin chain variable domain in the duodenum, jejunum, ileum cecum, colon, rectum and/or anal canal, respectively.

72. The method of claim **64**, wherein the stability of the HIS-substituted immunoglobulin chain variable domain is increased by at least 5%, more suitably 30%, more suitably 50%, relative to the stability of said progenitor-immunoglobulin chain variable domain, after 1 hour incubation in the Standard Human Faecal Supernatant Intestinal Tract Model.

73. The method of claim **64** wherein the EC50 of the HIS-substituted immunoglobulin chain variable domain is increased by no more than 400% relative to the EC50 of said progenitor immunoglobulin chain variable domain.

74. The method of claim **73** wherein the EC50 of the HIS-substituted immunoglobulin chain variable domain is increased by no more than 200% relative to the EC50 of said progenitor immunoglobulin chain variable domain.

75. The method of claim **74** wherein the EC50 of the HIS-substituted immunoglobulin chain variable domain is increased by no more than 50% relative to the EC50 of said progenitor immunoglobulin chain variable domain.

76. The method of claim **75** wherein the potency of said the HIS-substituted immunoglobulin chain variable domain is at least the same as the potency of said progenitor immunoglobulin chain variable domain.

77. The method of claim **64**, wherein the progenitor immunoglobulin chain variable domain is selected from the group consisting of a VHH, a VH, a VL, a V-NAR, scFv, a Fab fragment and a F(ab')2 fragment.

78. The method of claim **77**, wherein the progenitor immunoglobulin chain variable domain is a VHH.